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DEPARTMENT OF GENETICS
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Cables STANMED

Dr. Peter Sneath
Medical Research Council
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The Ridgeway, Mill Hill
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Dear Peter:

This reply to your letter of 9 June is probably far too late to be consequential for the paper on episomes, but in any case, my comments would be mainly for your interest, and would hardly be likely to evoke a strenuous effort at a revision though you may wish to use your own judgement about this.

Let me answer another point first of all, that λV2 is now doubtless much better to find in Jacob's system than was the λ2 of our earlier work, and since so much genetic work has been done with the Paris strains, I believe that I would recommend that you use them for any further developments. In our own early work we did not have the analytical techniques by which we might have distinguished different variants of the V2 phenotype.

May I note also that the address of our department is in the medical school at Palo Alto, not Stanford, California.

To the paper --

As Jacob will now acknowledge, the term episome was rather remarkably anticipated by Thompson. The reference to this is appended.

Page one, lysogenic bacteriophage, line six - the antecedent for "this" might be clarified.

Page two, other episomes, line one - "known" or "inferred"?

Page three, distribution of bacterial episomes, second paragraph, line two - is it really a definitive characteristic of episomes that they are infectious? or that they can be removed by acridine? Perhaps I am interpreting the term "common" too stringently.

Page four, second paragraph, RNA episomes - I don't see the implication that episomes can also contain RNA since Zinder's phage has by no means been proven to be episomic. This is, of course, an interesting possibility.

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The number of episomes per cell, line two - "one episome in the cell" - perhaps in the nucleus or chromosome, but the cell may contain several of these.

Page five - Adelberg has some more recent evidence on phosphorous starved F+ cells, that they are readily disinfected by the contagion of F; from which he concludes that under these conditions there is one F particle per cell. He believes that there may also be a more definite regulation in the segregation of the determinants. There is also an interesting note on this point in a recent issue of the Canadian Journal of Genetics and Cytology, I believe by James.

Effective episomes on the cell, line four - I do not accept that Maccacaro and Colombo had demonstrated a surface antigen characteristic of male cells. They had shown that such cells were more agglutinable by coli antisera. They did, of course, themselves, make the claim which I would here contest, and which has, of course, been fully substantiated by the Orskovs.

Page six - I was interested in your remark about the metabolism of F+ and F- cells. Cavalli has mentioned something to the effect that one of his students had found it different during mating and I will have to ask him more about this.

Page six, paragraph four - It might be worth noting that the Bhaskaran's F factor also seems to be a cinogen. If the point is not clear, Bruce might be able to elaborate on it.

Page eight, second paragraph - "In all three cases and unlike bacteriophage"- is this good syntax?

Page ten, Richter - I think his paper is now in press in Genetical Research. Third paragraph, line one - "classic", please! think of a better cliche than that.

Page eleven, second line from bottom - analogous. Last line - is this datum correct?, i.e., do capital I and capital e^I reinforce one another?

Page thirteen, second paragraph - the same point is perhaps even more ancient, see for example, my review in "Physiological Reviews", October, 1952, and, among others, a reference to a paper by Green which I append. My Nobel lecture (Science, 1960) is also preoccupied with the same issues, and I am rather surprised, frankly, that you had overlooked this discussion. I would

agree in placing special emphasis on the modification of surface properties by some of the episomes. We might consider the following gradation - that in bacteriophages a complete envelope is formed around the genetic material; that the colicinogens engender a fairly general modification of the cell wall lending it toxic properties (on this point see Gerbal and Barry); while the F particle generates a specific, and I'm inclined to think a local modification of the cell wall. In fact, one could explain the fact that the point of attachment of the F particle on the chromosome is the last to be transmitted in conjugation, if this chromosomally fixed F were in fact anchored to the wall. It is hard, in fact, for me to think of any alternative and plausible explanation for the polarity of chromosome transfer. If this paper is intended to be a balanced historical review, as I suspect it will be taken as, you might ask yourself whether the episome concept was not, infact, fully laid out in Esther's 1953 paper on lysogenicity, that it was then subsequently attacked by Wolman and Jacob as a misinterpretation of sexual polarity, and then was only finally regularized with the recrudescence of the term episome. I rely entirely on your own sense of propriety in dealing with this question; if the review is not intended to establish the historical development of the subject, you might be content with the present format of the manuscript.

Other work is going well - the laboratory is now almost completely converted to work on bacillus subtilis. We have been very pleased to have another one of your compatriots to maintain our long tradition, and Walter Bodmer, from Cambridge is now busily working on the kinetics of inactivation of transforming DNA by nucleases. He asked me some questions recently about penicillinase, and this moves me to ask you whether you have considered any tangible work on the genetics of penicillinase in the transformable strains of B. subtilis. Very likely we have discussed this before, but the details escape my memory at the present time, and while I do not think we would in any case make any hasty moves in that direction, I would be interested to know what your inclinations or results have been along these lines.

Mel Fradkin (an erstwhile graduate on para-mutation in corn under Brenk) has also been working here and in a perhaps not very brilliant experiment has shown that competent cells lose their capacity to take up DNA (while retaining their viability) upon treatment with periodate. It's not clear that this shows us any more about the mechanism of competence than it does of conjugation in E. coli, but we are following this up. A perhaps more important, though by no means as reliable a finding, is that under some conditions periodate will also inactivate the DNA for which there seems to be no good chemical excuse, but this might still be a fluke, although we are reminded of McCarty's studies on the inactivation of DNA by other oxidizing agents many years ago.

With fond regards to Joan and yourself

Yours sincerely,

Joshua Lederberg